REMARKS

I. Support for the Amendments

Claim 4 has been amended. Support for claim 4 as amended can be found throughout the original specification as filed. More particularly, support for amended claim 4 can be found from page 12, line 31, to page 15, line 27, and in the Examples.

II. Status of the Claims

Claims 1-14 were originally filed with the application and were subject to a restriction requirement. Claims 1-4 (Group I) and species CYP3A4 were elected. Claim 5-14 have been previously withdrawn.

In the Office Action, dated 3 October 2003, the Examiner rejected claims 1-3 and objected to claim 4 as being dependent upon a rejected base claim, but asserted that claim 4 would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

While Applicants disagree with the Examiner's rejection, they wish to proceed expeditiously with the prosecution of the application.

Accordingly, Applicants hereby cancel claims 1-3 without prejudice to the pursuit of these claims in an appropriate continuation or divisional application.. In addition, Applicants hereby amend claim 4 to include all of the limitations of claim 1, upon which it is dependent.

III. Rejection of Claims 1 and 2 Under 35 U.S.C. § 112, First Paragraph, Is Rendered Moot

The Examiner has rejected claims 1 and 2 under 35 U.S.C., first paragraph (p. 2). The Examiner alleges:

> Rejection of Claims 1 and 2 under 35 U.S.C. 112, first paragraph, for the reasons described in the prior action, is maintained.
>
> Applicants provide the following arguments in support of their request for withdrawal of said rejection. That, cells to be used in the instant invention should not be limited, for example, to HepG2 cells because the present invention makes it possible to evaluate total metabolism and oxidative metabolism by stable expression of cytochrome P450. That, examples of other liver-derived cells, such as HLE, PLC/PLF/5, HuH-6, HuH7, Hep3B, and the like are known in the art and may be useful in the practice of the invention. These arguments are not found to be persuasive for the following reasons.
>
> It is acknowledged that cells, other than HepG2, may be useful for the instant invention. However, Miyazaki et al. teach that HepG2 cells are "chromosomally abnormal, with a modal number of 55, and contain distinctive rearrangement of chromosome 1" (in IDS, pg. 203, col. 2, lines 1-2). Said teachings indicate that HepG2 cells are not the same as every other hepatocarcinoma cell line; thus, the utility of HepG2 cells for analysis of heterologous P450 enzymes may not be shared by all other hepatocarcinoma cell lines. The specification and knowledge in the art fails to provide sufficient guidance for how a person of ordinary skill in the art would select those cell lines that are useful without screening all lines derived from any human hepatocarcinoma cell. Such screening represents undue experimentation. Applicants' disclosure in their rebuttal that, the HLE, PLC/PLF/5, HuH-6, HuH7, and Hep3B cell lines are useful in the instant invention can not be considered as guidance, as said cell lines are not disclosed in the specification. Therefore; rejection of Claims 1 and 2 under 35 U.S.C. 112, first paragraph, for the reasons described in the prior action is maintained. (Pp. 2-3; emphasis in original.)

Applicants respectfully disagree with the Examiner's rejection of claims 1 and 2. In view of the Applicants' desire to proceed with the prosecution of the application with dispatch, however, Applicants have canceled claims 1 and 2 (without prejudice to the pursuit of the subject matter of these claims in an appropriate continuation or divisional application), thereby rendering the Examiner's rejection moot.

IV. Rejection of Claims 1-3 Under 35 U.S.C. § 103(a) Is Rendered Moot

The Examiner has rejected "Claims 1-3 under 35 U.S.C. 103(a)" (p. 3) as unpatentable over Dai et al. (1993) in view of GenBank Acc# J04449 (1994) and further in view of Waxman et al. (1991).

The Examiner alleges:

> Applicants provide the following arguments in support of their request for withdrawal of said rejection. That, a gene transfer system using vaccinia virus is usable for transient expression, which is totally different from a stable or constitutive expression system. That, the possibility of stable expression of CYP3A4 cannot be suggested by transient expression of CYP3A4 using vaccinia virus. That, the choice of a plasmid-mediated method has a sound technical basis and is not merely a matter of convenience. That, the plasmid-mediate method of Dai et al. is more difficult to utilize that the method using a vaccinia virus. That, there is no motivation in Waxman et al. or in Dai et al. to combine these two references to establish the stable expression of CYP3A4 using HepG2. These arguments are not found to be persuasive for the following reasons.
>
> It is acknowledged that expression of heterologous genes with viruses is different from expression with plasmids. A person of ordinary skill in the art would know the advantages and disadvantages of both approaches. Said person of skill, upon learning the teachings of Waxman et al., would know the advantages of using plasmids, instead of vaccinia virus, to stably express CYP3A4 in HepG2 cells. As applicants point out, the use of stable expression systems provides the benefits of observing metabolic activities in living cells; said benefits would be of common knowledge to a person of skill in the art. The Examiner does not agree that the plasmid-mediated method of Dai et al. is more difficult to utilize that the method using a vaccinia virus. Preparation and storage of viruses is much more difficult than preparation and storage of plasmids. Using viruses, new cells must be reinfected for each experiment; thus, both virus and infected cells must be prepared for each experiment. IN contrast, using plasmids, cells are transfected only once and readily available for experimentation. This ease of propagation and the obvious experimental benefits of stable transfection with plasmids, provide clear motivation to use the plasmid-mediated methods of Dai et al. to stably express CYP3A4 in HepG2. Appreciation of such motivation would be common knowledge to a person of ordinary skill in the art. Thus Rejection of **Claims 1-4** under 35 U.S.C. 103(a) as being unpatentable over Dai et al., 1993 in view of GenBank Acc# J04449, 1994 and further in view of Waxman et al., 1991 is maintained. (Pp. 3-4; emphasis added.)

First, Applicants assume, in light of the Examiner's remarks concerning the allowability of an amended claim 4, that only claims 1-3 have been rejected. Applicants respectfully request confirmation accordingly.

Second, Applicants respectfully disagree with the Examiner's rejection. In view of the Applicants' desire to proceed with the prosecution of the application with dispatch, however, Applicants have canceled claims 1-3 (without prejudice to the pursuit of the subject matter of these claims in an appropriate continuation or divisional application), thereby rendering the Examiner's rejection moot.

V. Objection to Claim 4 is Accommodated

The Examiner stated the following with respect to allowable subject matter and claim 4:

> Claim 4 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. (P. 4.)

To hasten the prosecution of the case, Applicants have canceled all remaining non-withdrawn claims without prejudice to their pursuit in an appropriate continuation or divisional application. Applicants hereby amend claim 4 to include all of the limitations of base claim 1, upon which claim 4 was dependent, in accordance with the Examiner's instructions.

Applicants respectfully submit that amended claim 4 is in condition for allowance and respectfully request allowance of the application accordingly.

VI. Conclusion

In view of the foregoing amendments and remarks, the present application is respectfully considered in condition for allowance. An early reconsideration and notice of allowance are earnestly solicited.

It is believed that all outstanding rejections have been addressed by this submission and that all the claims are in condition for allowance. If discussion of any amendment or remark made herein would advance this important case to allowance, the Examiner is invited to call the undersigned as soon as convenient.

If a petition for an additional extension of time is required, then the Examiner is requested to treat this as a conditional petition for an additional extension of time. Although it is not believed that any additional fee (in addition to the fee concurrently submitted) is required to consider this submission, the Commissioner is hereby authorized to charge our deposit account no. 04-1105 should any fee be deemed necessary.

Respectfully submitted,

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